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Clinical practice guidelines for the surgical management of colon cancer: a consensus statement of the Hellenic and Cypriot Colorectal Cancer Study Group by the HeSMO*

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Abstract

Despite considerable improvement in the management of colon cancer, there is a great deal of variation in the outcomes among European countries, and in particular among different hospital centers in Greece and Cyprus. Discrepancy in the approach strategies and lack of adherence to guidelines for the management of colon cancer may explain the situation. The aim was to elaborate a consensus on the multidisciplinary management of colon cancer, based on European guidelines (ESMO and EURECCA), and also taking into account local special characteristics of our healthcare system. Following discussion and online communication among members of an executive team, a consensus was developed. Statements entered the Delphi voting system on two rounds to achieve consensus by multidisciplinary international experts. Statements with an agreement rate of ≥80% achieved a large consensus, while those with an agreement rate of 60-80% a moderate consensus. Statements achieving an agreement of <60% after both rounds were rejected and not presented. Sixty statements on the management of colon cancer were subjected to the Delphi methodology. Voting experts were 109. The median rate of abstain per statement was 10% (range: 0-41%). In the end of the voting process, all statements achieved a consensus by more than 80% of the experts. A consensus on the management of colon cancer was developed by applying the Delphi methodology. Guidelines are proposed along with algorithms of diagnosis and treatment. The importance of centralization, care by a multidisciplinary team, and adherence to guidelines is emphasized.

Keywords Colon cancer, surgery, guidelines

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*HeSMO: Hellenic Society of Medical Oncology

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Introduction

During at least the last two decades and despite improvements in diagnosis, staging, local surgical treatment, and adjuvant therapy of colon cancer, there has been no significant improvement in oncological outcomes, at least to the extent seen for rectal cancer. Furthermore, in Europe 5-year survival rate ranges between 32% and 64% [1-3]. This

could be attributed to misuse of the new therapeutic and surgical modalities, the variety in the therapeutic strategies pursued, and failure to comply with the optimum evidence-based clinical practice guidelines and audit registries [3].

Aim

Driven by the Hellenic Society of Medical Oncology (HeSMO) a selection of an executive team was made on the grounds of their experience in colorectal cancer. The executive team was assigned to elaborate and develop a consensus document and form guidelines on the main aspects of image staging, surgical treatment and follow up of colon cancer, based on the review of literature and the principles of the evidence-based medicine.

In the present study, the guidelines on the management of colon cancer only are presented. Guidelines on: a) molecular biology, genetics, prognostic and predictive markers, hereditary forms, surveillance; b) rectal cancer care; c) adjuvant treatment of colorectal cancer; and d) management of metastatic colorectal disease are presented elsewhere.

Legal disclaimer

HeSMO considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient's individual circumstances. In view of the consulting and non-binding nature, these guidelines cannot form the basis for legal action or litigation for compliance or absence of compliance in the clinical practice setting, but can only be considered as general guidelines based on best available evidence for assistance in decision-making.

Any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. HeSMO makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

In addition, these guidelines describe evaluations and administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative management strategies in a disease for which better treatment is sorely needed. However, by reviewing and synthesizing the latest literature, these practice guidelines serve to identify questions for further research and the settings in which investigational therapy should be considered.

Methodology

At the first stage, background discussion, statements and recommendations, updating, amendments and drafting were processed at meetings and through online communication of the members of the executive team for feedback, from February 2011 to August 2013. Levels of evidence (LOE) and grades of recommendations have been presented according to their strength (strength of recommendation, SOR) (Table 1), based on the version adopted by the ESMO Consensus Guidelines for colorectal cancer [4]. From the final draft, which was circulated for editing to all members of the executive team, statements were drawn as key single sentences.

Thereafter, consensus on statements was developed, by using Delphi methodology [5], which involved two consecutive rounds of anonymous online voting and feedback by experts. Anonymous voting ensured that no external pressure was exerted during decision-making. Circulation of feedback from the voting rounds prevents strong opinion makers dominating the direction of the statement. Experts were identified from a systematic search of published literature and recommendations of other experts. An expert was defined as a physician who contributes to multi-disciplinary team managing patients with colon cancer.

The first round of the online voting process opened on September 29th, 2013 and closed on December 6th, 2013. At voting, options were to agree, disagree or abstain. Abstaining votes were intended for non-experts and did not count towards the overall percentage agreement. Statements achieving an agreement of 80% or more were considered as having reached consensus and were subjected to minor refining editing, after being circulated among the members of the executive team. Those statements achieving an agreement of less than 80% were considered as having

Table 1 Level of evidence and strength of recommendation

Level of evidence	
I	Evidence from at least one large randomized controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity
II	Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts' opinions
Strength of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs) optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

RCT, randomized controlled trial

achieved low consensus and were subjected to major revision and amendments, again after being circulated among the members of the executive team, and then entered a second round of the online voting process by the experts. The second round opened on January 6th, 2014 and closed on January 24th, 2014. In the final document all statements are presented as recommendations of care. Even statements achieving a low consensus of <80% were included. At the end of each recommendation the LOE and the SOR are mentioned, followed by the rate of voting consensus (ROVC).

Results

Sixty-one statements entered the Delphi methodology, where 109 experts-voters participated. The median abstain rate was 10% (0-41%). After the first voting process, five statements achieved voting consensus by all participants, and there were 47 statements achieving an over than 90% consensus. Three statements that achieved a rate of consensus of less than 80% and another one achieving 81% entered a second round of voting, after being amended by the executive team. In the end of the process, all four statements improved their ROVCs, and there were no statements with a ROVC less than 80% (Table 2).

General considerations

Background

Optimum therapeutic strategy and adequately executed surgery is best produced in volume-based referral centers by an adequately trained multidisciplinary team (MDT) which should include surgeons, radiologists, medical oncologists and pathologists. Further to centralization and adherence to clinical guidelines, oncological outcomes are expected to improve by national audit registries [2,4,6]. It should be mentioned that guidelines do not always derive from high quality level I data, and therefore should be applied with caution.

Table 2 Rate of voting consensus of statements after the two voting processes

Rates of voting consensus	Number of statements after first voting process	Number of resubmitted statements	Number of statements at the end of process
100%	5		7
90-99%	43		45
80-89%	8	1	9
70-79%	3	3	
Newly introduced statement		1	
	Total: 60	Total: 5	Total: 61

Table 3 Initial staging of colon cancer

Aim	Modalities
Confirmation of diagnosis	Endoscopy - biopsies
	Histopathological examination
Localization of tumor and synchronous lesions	Endoscopy - tattooing of lesion
	MDCT
	MDCT colonography (in obstructive lesion)
	MRI (if sensitivity to iodinated contrast medium)
	Double contrast barium enema (last option)
T stage	MDCT
	MRI (if sensitivity to iodinated contrast medium)
N stage	MDCT
	MRI (if sensitivity to iodinated contrast medium)
M stage	
Liver	MDCT
	MRI (if sensitivity to iodinated contrast medium)
	(in equivocal cases)
	US (in equivocal cases)
	PET/CT (if MDCT, MRI, US inconclusive)
Lungs	MDCT
	Chest x-ray (second choice)
Bones (relevant symptomatology)	Scintigraphic scan
Brain (relevant symptomatology)	Scintigraphic scan

MDCT, multi-detector computed tomography; MRI, magnetic resonance imaging; US, ultrasound; PET/CT, positron emission tomography / computed tomography

RECOMMENDATION

1. Centralization, care by a MDT, adherence to clinical guidelines, and audit registries are necessary to improve oncological outcomes in the management of colon cancer (LOE IV; SOR A) (ROVC: 98%)

Preoperative staging

Clinical examination

Background

Physical examination and medical and family history of colorectal cancer, polyps and other cancers should be obtained. Further to assessment of the primary colonic tumor, total colonoscopy is mandatory to detect any synchronous lesions. Additional investigations like virtual colonoscopy or CT colonography could be helpful, even though they are not

Preoperative staging

Clinical examination

Background

Physical examination and medical and family history of colorectal cancer, polyps and other cancers should be obtained. Further to assessment of the primary colonic tumor, total colonoscopy is mandatory to detect any synchronous lesions. Additional investigations like virtual colonoscopy or CT colonography could be helpful, even though they are not yet standard procedures. These could be valuable to precisely locate the tumor, particularly useful for the surgical approach, especially in patients who are candidates for a laparoscopic resection. They could also help detect other synchronous colonic lesions or polyps if colonoscopy could not explore the whole colon due to an obstructive tumor [7].

RECOMMENDATIONS

2. Physical examination and relevant family history is strongly recommended (SOR A) (ROVC: 100%)
3. Total colonoscopy is mandatory to exclude synchronous lesions. When synchronous lesions are detected, biopsies are taken and removal may be attempted. If additional malignancy is present, therapeutic surgical strategy is modified accordingly (LOE III; SOR A) (ROVC: 96%)
4. If total colonoscopy has not been performed preoperatively, it can be attempted intra-operatively or at 3 months postoperatively (LOE III; SOR A) (ROCV: 87%)

Image staging (Table 3)

Background

Treatment strategy for colon cancer is guided by adequate staging. Complete colonoscopy and multi-detector computed tomography (MDCT) scan of the chest, abdomen, and pelvis should be performed. MDCT remains the main imaging modality for preoperative planning, metastatic liver lesion detection and tumor surveillance. MDCT accuracy rate for assessing lower stage lesions is not as good as that for advanced lesions. This discrepancy relates to the limited ability of MDCT to determine depth of bowel wall penetration. However, abdominal/pelvic MDCT has a high negative predictive value. The specificity for detecting lymph nodes involved with tumor is approximately 50%. In addition, the modality offers the ability of a rapid global evaluation and demonstration of complications (perforation, obstruction, etc.) that may not be clinically apparent [8,9]. Among patients with potentially resectable liver metastases and a negative initial chest x-ray, additional imaging with a chest CT may detect pulmonary metastases in up to 5% of patients [10].

Magnetic resonance imaging (MRI) has equal accuracy to MDCT for local staging of colonic neoplasms. Accuracy in identification of lymph node metastases is also equal to MDCT, and slightly superior for detection of liver metastases. MRI may be beneficial in determining involvement of the adjacent organs. MRI may also be considered in preoperative evaluation of patients with sensitivity to iodinated contrast material, particularly in the evaluation of the liver [8,11]. MRI and contrast-enhanced ultrasonography (US) should be considered as problem solving techniques for characterization of indeterminate liver lesions [8,9].

Computed tomographic colonography (CTC) can accurately identify all colorectal masses but may overcall stool as masses in poorly distended or poorly prepared colons. CTC has an overall staging accuracy of 81% for colorectal cancer and is superior to barium enema in visualizing colonic segments proximal to obstructing colorectal lesions. Furthermore, the method can identify synchronous lesions in patients with colorectal masses, and image the proximal colon in patients with obstructing colorectal lesions [8,12].

FDG-PET is not recommended for initial staging. It could be used in patients at high surgical risk when there is a strong probability of metastatic disease invisible on CT or MRI. However, the role of FDG PET/CT is not yet clear owing to the small number of studies [13]. Also, brain and bone scintigraphic scans are only indicated in patients with relevant symptomatology.

RECOMMENDATIONS

5. Minimal requirements for colon cancer staging are complete colonoscopy and MDCT of the abdomen and pelvis (LOE I, SOR A) (ROVC: 89%)
6. MDCT of the abdomen aims in identifying local extension of the tumor, intra-abdominal dissemination of the disease or and distant metastasis (LOE II; SOR A) (ROVC: 100%)
7. MDCT is of limited accuracy in the assessment of T1-3 stage, N stage, early peritoneal carcinomatosis, and small liver metastasis (LOE II; SOR A) (ROVC: 88%)
8. Lymph node involvement as assessed by MDCT is based on morphological characteristics, such as size and contour irregularity and heterogeneity (LOE III; SOR A) (ROVC: 94%)
9. MRI of the abdomen and pelvis is indicated as a problem solving technique (specifically for liver metastases) or if contrast MDCT is contraindicated (LOE I, SOR A) (ROCV: 95%)
10. Chest CT in all patients is recommended for the identification of possible lung metastases (LOE III, SOR B) (ROVC: 92%)
11. Virtual colonoscopy or CTC could be considered for detecting synchronous colonic lesions or polyps if colonoscopy could not explore the whole colon due to an obstructive tumor (LOE III, SOR B) (ROVC: 90%)

RECOMMENDATIONS

12. If total colonoscopy is contraindicated and CT is not available, a double contrast barium enema is indicated in cases without obstruction (LOE IV, SOR C) (ROVC: 83%)
13. FDG-PET should not be used routinely for initial staging (LOE II, SOR B) (ROVC: 93%)
14. Bone scan and brain imaging should only be performed for patients with relevant symptoms (LOE IV, SOR B) (ROVC: 95%)

Surgical treatment

Preoperative laboratory assessment

Background

A complete blood count is necessary to determine levels of hemoglobin. If hemoglobin is less than 8 g/100 mL increased postoperative morbidity is expected. A hemoglobin level of above 10 g/100 mL prior to surgery is desirable. This can be achieved either with blood transfusion at least 2-3 days prior to surgery or with the administration of erythropoietin and iron intravenous infusion at least two weeks preoperatively. There is evidence that blood transfusion impairs immune response of the patient to malignant process of the disease, which may translate to worse long-term oncological outcomes [14,15]. For this reason, erythropoietin and iron infusion is recommended as the safest choice in oncological terms, although relative evidence is not sound and recommendation level is low [16]. Defective clotting mechanisms should be corrected accordingly before surgery.

A baseline determination of serum carcinoembryonic antigen (CEA) level is necessary for the indirect detection of completeness of surgery, namely increased preoperative CEA levels should be normalized after curative surgery. Also according to a recent review [17], postoperative increase of serum CEA is a highly specific but insufficiently sensitive factor for the detection of local or distant recurrent colorectal cancer. A cut-off value of 2.2 ng/mL may provide the ideal balance of sensitivity and specificity. Therefore, serial serum CEA determination is highly recommended as a first-line surveillance test.

RECOMMENDATIONS

15. Hemoglobin blood level should ideally be >10 g/100 mL and clotting mechanisms corrected if impaired prior to surgery (LOE II, SOR A) (ROVC: 97%)
16. Preoperative baseline determination of serum CEA levels is recommended as a first-line surveillance test (LOE III, SOR A) (ROVC: 95%)

Bowel preparation

Background

There is substantial evidence that mechanical bowel preparation prior to elective colectomy does not offer any advantage over surgery without bowel preparation [18-20]. As a matter of fact and according to a recent meta-analysis, mechanical bowel preparation may be associated with increased rate of anastomotic leak and wound infection [18].

RECOMMENDATION

17. Mechanical bowel preparation is not generally indicated (LOE I, SOR A) (ROVC: 86%)

Enhanced recovery programs

Background

Implementation of enhanced recovery programs, so called "fast-track", in colorectal surgery for both benign and malignant diseases reduces physiological and psychological stress, accelerates normalization of gastrointestinal function, improves postoperative physical status, and most importantly is associated with less morbidity and shorter postoperative hospital stay. In addition, implementation of those programs does not necessitate specific equipment nor does it require increased costs. Therefore, implementation of "fast-track" is strongly recommended in units with motivated and adequately trained personnel [21-23].

RECOMMENDATION

18. Implementation of enhanced recovery programs is strongly recommended, because it is associated with less postoperative morbidity and faster recovery (LOE I, SOR A) (ROVC: 100%)

Surgical treatment

Background

Malignant polyp

Treatment of the malignant colonic polyp depends on clinical and histopathological features:

i) endoscopic removal of a colonic polyp that proves to be malignant may be an adequate treatment in case of an early cancer [with clear margins (>3 mm)] with low risk features (low grade, no invasion of lymphatic vessels), which indicate low risk for lymph node invasion and distant metastasis
ii) endoscopic removal may also be adequate treatment for a pedunculated polypoid cancer with low risk features in which invasion involves the head and spares the stalk and the basis
iii) in case of a R0 excision of an early cancer with high-risk features (sessile polyp, high grade, invasion of the

submucosa -sm2/3-, invasion of lymph or venous vessels, tumor budding) a definite treatment in terms of colectomy is recommended

iv) removed colonic polyps baring a ≥T2 tumor, with or without clear margins of resection should be also subjected to definitive surgical treatment.

An intense schedule of follow up is recommended in patients with a removed malignant polyp and no further treatment (Table 4).

RECOMMENDATIONS

19. For stage 0 (TisN0M0) and T1, N0, M0 low-risk tumors, local excision or simple polypectomy with clear margins by colonoscopy could be performed, preferably in patients with severe co-morbidities (LOE II, SOR A) (ROVC: 99%)
20. If excised malignant polyp shows high-risk features, definitive surgical treatment is recommended (LOE IV, SOR A) (ROVC: 97%)

Table 4 Management of the malignant colonic polyp

Stage	Risk factors	Management
Tis, T1, Nx, M0	Low	Follow up
	sm1, L0, V0, PN0	
	Clear resection margins (>3 mm)	
	Low grade	
T1, Nx, M0	Low	Follow up
	Pedunculated, spared stalk	
	L0, V0, PN0	
	Low grade	
T1, Nx, M0	High	Colectomy
	Sessile	Complete mesocolic excision
	Inadequate resection margin	
	sm/3, L1, V1, PN1	
T≥2, Nx, M0		Colectomy
		Complete mesocolic excision

Resectable non-obstructing lesion (Fig. 1)

Background

For early cancer stage 0 or partly stage I (T1) local excision by means of the colonoscope could be considered, particularly in patients with increased co-morbidities. If histology shows clear margins of resection, well-differentiated tumor (G1, G2) and no lymphatic invasion, an expectant policy is recommended, as local recurrence is not very likely and lymph node metastasis may occur in only up to 4%. In case histology shows incomplete resection margins, a poorly differentiated lesion (G3, G4) or lymphatic invasion, surgical curative resection should follow, as local recurrence is very likely and lymph node metastasis may occur in up to 20% of the cases [24].

For resectable colonic carcinoma, the oncologically optimal surgical procedure is a curative (R0) colectomy with adequate proximal and distal resection bowel margins, and *en-bloc* complete removal of the respective to the resected segment mesocolon (Complete Mesocolic Excision - CME) with all regional lymph nodes [25-27]. Based on the fact that potential involvement of pericolic lymph nodes does not extend the 8 cm proximal and distal to the tumor baring bowel segment, bowel resection margins should be at least 10 cm, unless this is restricted by the exact location of the tumor or/and type of colectomy [28,29]. As a general rule, proximal ligation and division of the vascular stems supplying the specimen to be resected (central vascular ligation, CVL) ensures CME and the highest possible retrieved number of lymph nodes [26,27].

For tumors situated at the cecum and ascending colon, CVL involves the ileocolic vessels and the right branches of the middle colic vessels. For tumors situated at the right side of the transverse colon, CVL involves the ileocolic and the middle colic vessels. For tumors situated at the middle and left transverse colon and the upper descending colon, CVL involves the middle colic vessels, the ascending branches or

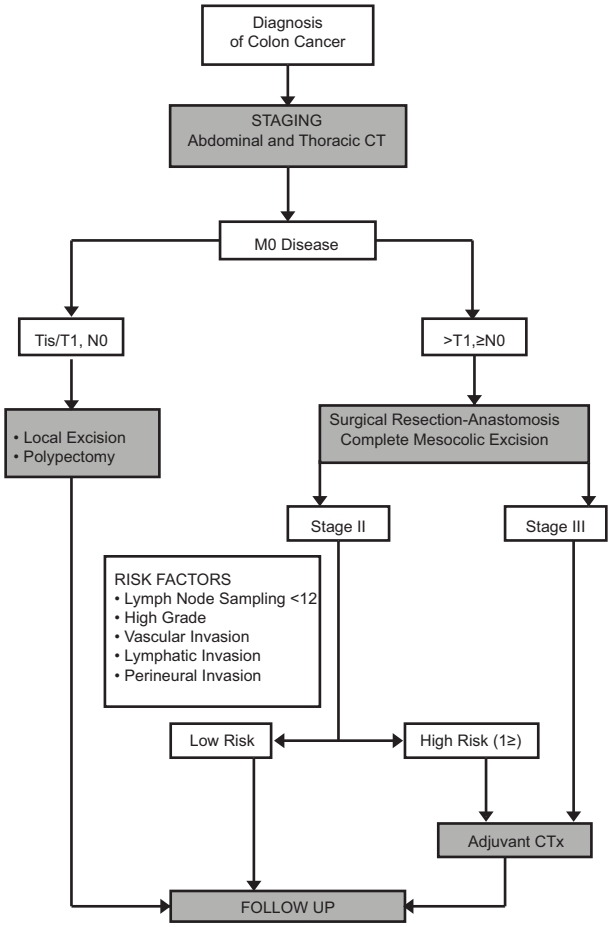

Figure 1 Strategy and treatment algorithm of non-metastatic colon cancer
CT, computed tomography; CTx, chemotherapy

the stalk of the ileocolic vessels and the ascending branches of the left colic vessels. For tumors situated at any site from the descending colon to the rectosigmoid junction, CVL involves the division of the inferior mesenteric artery at 1 cm distal to its origin from the aorta and the inferior mesenteric vein just below the lower border of the pancreas [26,27].

Resection should be complete in terms of removal of all regional to the resected bowel segment lymph nodes. A resection is considered incomplete (R2) if involved lymph nodes are not removed. The number of the lymph nodes removed depends on the location of the tumor [30]. In general, right colon segments tend to contain much higher numbers than the left ones. According to UICC recommendations [31], at least 12 lymph nodes are required to be examined for the staging of the disease. If all lymph nodes examined are negative but <12 in number, staging is not optimal and safe. The accuracy of staging of colorectal cancer parallels the number of removed lymph nodes [32]. There are two additional reasons emphasizing the significance of the number of removed lymph nodes: i) increased number of removed lymph nodes is associated with improved survival, irrespective of the nodal status [33]; ii) the ratio of the metastatic to total number of removed nodes is inversely related to recurrence and overall survival [34]; and iii) increased absolute number of negative retrieved nodes is associated with better oncological outcomes even in stage III disease. The latter two stand true only when the number of examined nodes is >12 [30,35-39].

Anastomosis to reestablished bowel continuity could be performed with use of sutures or stapling devices. Current evidence shows that there are no differences in the anastomotic leak or stenosis rates between the two approaches [40]. Possibly stapled ileo-colic anastomosis may be associated with fewer anastomotic leaks than those hand sewn [41]. There is also no difference in the anastomotic complication rate between single and double-layer sutured anastomosis [42].

RECOMMENDATIONS

21. The non-obstructing colonic cancer should be treated by surgical resection, irrespective of stage (LOE I, SOR A) (ROVC: 83%)
22. A curative resection (R0) of the non-obstructing colonic cancer involves removal of the tumor baring colonic segment with adequate proximal and distal margins, central ligation and division of the supplying vessels and removal of the attached mesocolon (CME). The exact length of bowel removed, vessels ligated and divided and mesocolon removed depends on the exact location of the tumor (LOE III, SOR A) (ROVC: 98%)
23. In case of colon cancer invading adjacent organs (T4b), *en-bloc* R0 resection of colon and involved organ should be attempted (LOE III, SOR A) (ROVC: 100%)
24. Anastomosis can be fashioned with sutures or stapling devices, without significant differences in the anastomotic complication rate (LOE I, SOR A) (ROVC: 95%)

Laparoscopic approach

Background

Laparoscopic colectomy is nowadays the alternative to the open approach. There is substantial evidence based on several comparative studies that the laparoscopic approach for colon cancer surgery is as effective and as safe as the open one. Several meta-analyses and systematic reviews [43-49] including among others three large multicenter randomized comparative trials: the COST trial in the USA involving 872 patients [50-52], the CLASICC trial in the UK involving 794 patients [53,54], and the COLOR trial in Northern Europe involving 1248 patients with colon cancer [55], plus several other single-center comparative randomized trials [56-59] clearly show that the laparoscopic approach is associated with faster recovery, less postoperative pain and use of narcotic analgesics and less immediate postoperative morbidity as compared to the open approach. Furthermore, quality of surgery, as depicted in the percentage of involved resected margins and the number of retrieved lymph nodes, is similar between the two approaches. Also, local recurrence and overall and disease-related survival are similar between the two approaches. Finally, and in the long run, there is less readmission rate due to obstructive ileus [60] and lower incidence of incisional hernias [61,62] after the laparoscopic than after the open approach. It has been recently shown that laparoscopic colectomy works perfectly with enhanced recovery programs, offering even better faster recovery and less immediate postoperative morbidity [63-65].

It is recommended that laparoscopic colectomy for cancer should be performed by experienced surgical teams with adequate case volume, a necessary factor for improved outcomes [66]. Conversion to open, particularly when performed at a late stage of the procedure, may be associated with increased postoperative morbidity as compared to both the laparoscopically completed and the open approach. The main predictive factors for conversion are the T4 large tumors, the increased ASA condition of the patient, obesity and surgeon's limited experience [67]. Preoperative image staging is mandatory to identify T4 tumor or tumors >8 cm which should be amenable only to the open approach. Previous surgery and advanced age are not contraindications to laparoscopy. Also, it should be considered that obesity, though not an absolute contraindication, is associated with increased rate of conversion. Tumors not invading the bowel wall and unlikely to be visually identified at laparoscopy should

RECOMMENDATIONS

25. Laparoscopic surgery for uncomplicated cancer of the right and left colon offers faster recovery and less morbidity as compared to the open approach. Oncological results are similar between the two approaches, provided that the surgical team involved is well trained and serves a large volume of cases (LOE I, SOR A) (ROVC: 96%)

26. Laparoscopic resection of tumors of the transverse colon may be technically demanding and the quality of specimen may not be optimal due to difficult dissection, ligation and division of the middle colic vessels at their origin (LOE III, SOR A) (ROVC: 93%)
27. Laparoscopic approach is not indicated for bulky and advanced colon lesions, where curative resection can be achieved by open surgery (LOE I, SOR A) (ROVC: 94.5%)
28. Small lesions not visible by laparoscopy should be marked prior to surgery (LOE III, SOR A) (ROVC: 99%)
29. As conversion may be associated with increased morbidity as compared both to laparoscopically completed and to open approach, predictive factors for conversion, such as obesity or ASA III- IV cases, should be identified prior to laparoscopy (LOE II, SOR B) (ROVC: 92%)
30. Early or pre-emptive as opposed to late conversion does not seem to be associated with increased morbidity (LOE IV, SOR B) (ROVC: 89%)

be marked with Indian ink prior to surgery or localized with an on -table colonoscopy. The laparoscopic approach is not recommended for carcinomas located at the transverse colon, because dissection of the middle colic vessels is very difficult and laborious and quality of specimen is not optimal [68]. The laparoscopic approach is not recommended in acutely perforated or obstructing colonic tumors.

Macroscopic specimen assessment

Background

Quality of the resected colonic specimen by either approach should be assessed macroscopically. The procedure involves spread but not stretching of the specimen on paper or towel

RECOMMENDATIONS

31. The quality of the resected specimen should be macroscopically assessed and photographed prior to fixation (LOE III, SOR B) (ROVC: 98%)
32. Any macroscopic perforation at the tumor site should be noticed (SOR A) (ROVC: 100%)
33. Distal and proximal bowel margin should be measured on the spread fresh specimen (LOE III, SOR B) (ROVC: 95%)
34. The macroscopic quality of the specimen is assessed regarding integrity of peritoneal and fascial-mesothelial surfaces, and classified as mesocolic, intramesocolic and intramuscularis (LOE III, SOR B) (ROVC: 99%)
35. For adequate staging of the disease, at least 12 lymph nodes should be found in the resected specimen (LOE II, SOR A) (ROVC: 97%)
36. Removal of the highest possible number of lymph nodes is encouraged, as it is associated with better oncological outcomes in both stage II and III disease (LOE III, SOR B) (ROVC: 97%)

and at first photographed at both sides. Then completeness of mesocolon resection is graded (mesocolic, intramesocolic and intramuscularis). A mesocolic resection is associated with better survival as compared to intramuscularis [25-27]. Also, with the use of a ruler: i) the whole bowel and the proximal and distal to the tumor length, as well as the tumor length; ii) the distance of the central vascular tie to tumor; and iii) the shortest distance from the central vascular tie to the bowel wall are measured [27].

Resectable non-obstructing synchronous bowel carcinomas

Background

Synchronous carcinomas of the colon are resected in the form of one specimen and one anastomosis is established. Segmental colonic resection with multiple anastomoses should be avoided, as they are associated with increased morbidity. When one of the carcinomas is located at the right colon, an extended right hemicolectomy is recommended. Likewise, when two lesions are located at the left colon, a left hemicolectomy is recommended. The procedure can be performed by either open or laparoscopic approach in selected cases.

RECOMMENDATION

37. Extended colectomy with CME and CVL is indicated for synchronous non-obstructing colon lesions. Segmental colon resections with more than one colo-colonic anastomosis are not indicated (LOE III, SOR B) (ROVC: 91%)

Obstructing carcinoma

Background

For resectable colon cancer causing acute complete obstruction, resection with one or two stage anastomosis is recommended [69-72]. If the condition of the patient does not permit surgery, stenting, as a bridge procedure, for the

alleviation of the obstruction first and curative resection after two weeks is the management of choice [73-75]. However, evidence for the superiority of stenting in malignant colonic obstruction over emergency surgery is not sound, apart from a shorter hospital stay, a less procedure duration and less blood loss [76].

If the obstructing carcinoma is unresectable, palliative surgery in the form of defunctioning proximal stoma or insertion of a stent is recommended. If the general condition of the patient permits it, chemotherapy and/or radiotherapy could be added [77].

RECOMMENDATIONS

38. Obstructing resectable colonic tumors are treated with one- or two- stage curative colectomy with colo-colonic anastomosis depending on the clinical status of the patient and surgeon's preference (LOE II, SOR A) (ROVC: 96%)
39. For patients who cannot undergo surgery for a resectable obstructing colonic tumor, stenting of the lesion is an alternative solution (LOE IV, SOR B) (ROVC: 97%)
40. Obstructing unresectable colonic tumors are palliated by chemotherapy, invasive techniques and supportive care (LOE IV, SOR B) (ROVC: 90%)

Hereditary non-polyposis colon cancer (HNPCC)

Background

Considering that HNPCC patients are younger in age than those with sporadic colon cancer and probability to develop metachronous lesions is very high, a total colectomy is recommended [78-80].

RECOMMENDATION

41. For colon cancer on the basis of HNPCC, total colectomy is indicated, particularly in the young patients, where metachronous lesions are highly likely to develop (LOE III, SOR A) (ROVC: 94%)

Logoregional recurrence

Background

Definition, incidence, risk factors

Reports on local recurrence of colon cancer after curative resection are limited and, as a result, incidence, risk factors and clinical presentation of the condition are not well defined. Even definition of locoregional recurrence is poor, and may involve primarily the anastomosis, but also the mesenteric lymph nodes, the peritoneum or even the retroperitoneal space. A more comprehensive definition of locoregional recurrence is the recurrence at the abdominal quadrant of primary tumor location [81-84].

According to a population-based study [83], the incidence of recurrence after potentially curative resection of colon cancer was 11.5% at 5 years. Most of the recurrences were anastomotic. According to the same study, emergency conditions, namely perforation or obstruction, at the initial presentation, are independent risk factors for recurrence, possibly because of technical difficulties and suboptimal primary surgery, as most of these procedures are performed by non-colorectal surgeons [83,85-88]. Also, advanced T and N stage, location of the primary tumor at the hepatic flexure or sigmoid, poor differentiation of the primary tumor, and suboptimal primary surgery with low number of retrieved lymph nodes are considered risk factors of recurrence [81-84]. More than 80% of the cases are discovered by symptomatology. In the remaining cases recurrence is found at the regular follow up, as anastomotic recurrence at endoscopy and increased serum CEA [81-84].

Imaging

CT is not very accurate for early detection of colon cancer local recurrence, due to the distorted local anatomy after operation. The reported sensitivity reaches only 53% for CT, while FDG-PET shows a much better sensitivity of 93% [83]. The typical PET/CT appearance is of a hypermetabolic soft tissue mass or subtle wall thickening at the anastomotic site, often identified by a surgical ring of radio-opaque staples. Although colonoscopy would be the ideal technique for diagnosing and confirming anastomotic site recurrences, FDG PET/CT imaging can prove to be an excellent noninvasive modality when such recurrences are suspected, specifically in the cases of extramural and/or nodal infiltration. At present, whole-body (18)F-FDG PET/CT is an advanced diagnostic imaging technique in detecting locoregional recurrence and metastases in postoperative patients with colonic carcinoma for its higher sensitivity and specificity [89-91]. MRI does not seem to offer an added value, since its sensitivity in identifying early postoperative colon cancer recurrence is relatively low. Whole-body diffusion-weighted MRI is being explored for recurrent colon cancer, however, there is currently no evidence to suggest that this functional technique can replace PET/CT [83,89].

Management

A MDT should evaluate patients with recurrence, although this is not usually the case, according to Sjoevall *et al* [83]. Surgery is offered in almost 60% of the cases, in combination with radiotherapy and chemotherapy. Palliative measures, including chemotherapy and radiotherapy, are reserved for the remaining cases [81-84].

Potentially curative resection can be achieved to approximately one fifth of those amenable to surgery. Most of potentially curative resections are elective. Only complete

RECOMMENDATIONS

42. Detection of locoregional recurrence is based on the increase in serum CEA concentration, endoscopic modalities and imaging with MDCT or MRI (LOE I, SOR A) (ROVC: 99%)
43. Prior to curative surgery for the locally recurrent disease, distant metastasis should be excluded with the use of imaging modalities, including PET-CT (LOE III, SOR A) (ROVC: 94%)
44. Preoperative chemotherapy may be administered to down-size and down-stage the recurrent lesion, and may convert a non-resectable lesion to a resectable one (LOE II, SOR A) (ROVC: 94%)
45. Only R0 resection should be attempted, as they are associated with reasonable oncological outcomes (LOE I, SOR A) (ROVC: 96%)
46. In case of synchronous metastatic disease, treatment is personalized, also depending on the features of metastatic disease (SOR A) (ROVC: 95%) (see guidelines for metastatic colorectal disease)

resections offer a survival rate of approximately 40% at five years, whilst none of the patients with recurrent colon cancer and incomplete or no resection survive 5 years [81-84].

Pathology

Background

If not *ex vivo* in the theater, macroscopic assessment of the fresh specimen is processed in the laboratory as described before. The lateral resection margin of the fresh surgical specimen must be inked. The surgical specimen is opened leaving intact the tumor area and 2 cm below and above it and is then fixed in formalin solution for 48 h.

The histology report must include:

A. Gross description which involves length of surgical specimen, tumor size (3 dimensions) distance from proximal or distal margin, depth of invasion, tumor perforation, other lesions not related with the tumor (Crohn's disease, ulcerative colitis, adenomatous polyp, familial adenomatous polyposis), and total number of lymph nodes. The distance of direct tumor spread outside the muscularis propria should be recorded and the area in which tumor spreads closest to the lateral resection margin should also be identified macroscopically.

B. Microscopic description: ***Histologic type.*** The main histologic types in WHO classification are adenocarcinoma, mucinous adenocarcinoma (>50% mucinous), signet ring carcinoma (>50% signet ring), squamous carcinoma, adenosquamous, small cell, medullary and undifferentiated carcinoma. Although most histological types do not have any proven prognostic significance there are exceptions. Signet-ring and small cell carcinomas have poor prognosis. Mucinous and medullary carcinomas, when associated with microsatellite instability (MSI), have a favourable prognosis [92,93].

Histologic grade. Currently, a 2-tiered grading system is used (low and high grade). The system is based on the proportion of gland formation and in this way the inter-observer variation is avoided. Low grade has a proportion >50% glandular formation and in this grade the well and moderately differentiated carcinomas are included. In the high-grade category the poorly differentiated and undifferentiated carcinomas are included (<50% glandular formation) [92-94].

Lymph nodes. All lymph nodes found in the surgical specimen should be sampled. It has been shown that a minimum of 12 lymph nodes must be found to predict the real lymph node status. The interpretation of the discrete nodules of tumor in the adipose tissue on microscopic examination is many times problematic. According to the old guideline, extramural tumor nodules measured >3 mm in diameter but lacked evidence of residual lymph node tissue were considered as positive lymph nodes. According to the updated guideline, a discrete extramural invaded nodule with smooth contours irrespective of size is considered as positive lymph node [92-95]. Extramural and extranodal tumor deposits at the mesenteric fat are considered as remote metastatic disease and carry a poor prognosis [96].

Blood, lymphatic vessel invasion, perineural invasion. Several studies have shown that extramural vascular invasion (blood or lymphatic) is of strong prognostic significance and is associated with increased risk of liver metastasis. The prognostic importance of involvement of small vessels in the submucosa has also been well documented in the polypectomies for malignant polyps and is associated with risk of lymph node metastasis. Extramural vascular invasion is recorded when tumor is present within a space lined by endothelium and/or surrounded by muscle, and when inside the space erythrocytes are observed. Studies have shown that the detection of venous invasion depends on the number of blocks taken from the tumor periphery. The College of American Pathologists recommends 3-5 blocks from the deepest part of the tumor to be examined [92,93]. Also, it has been shown that perineural invasion is an independent indicator of poor prognosis [92,93].

Tumor infiltrating lymphocytes. The intratumoral lymphocytic infiltration is associated with MSI, medullary architecture and is considered as a favorable prognostic factor [92,93].

pTNM classification. Colorectal cancer is classified according to the pTNM system [92-94] (Table 5).

Residual tumor classification. Surgical margin status should be reported. For the resection margins after surgery, the R classification system is advocated. Four grades are in use: Rx (presence of residual tumor cannot be assessed); R0 (no residual tumor - distance from closest involved margin must be reported; R1 (microscopic residual tumor); and R2 (macroscopic residual tumor) [92-94].

Assessment of pT1 colorectal tumor. pT1 tumors invade the muscularis mucosa and submucosa without invasion of muscularis propria. This group of tumors is often encountered

Table 5 pTNM classification

Primary tumor
Tx: primary tumor cannot be assessed
T0: no evidence of primary tumor
Tis: intraepthelial or intamucosal tumor
T1: tumor invades submucosa
T2: tumor invades muscularis propria
T3: tumor invades beyond the muscularis propria into: subserosa or into the nonperitonealized pericolic or perirectal tissues
T3a: minimal invasion <1 mm beyond border of muscularis propria
T3b: slight invasion 1-5 mm beyond border of muscularis propria
T3c: moderate invasion >5-15 mm beyond border of the muscularis propria
T3d: extensive invasion >15 mm beyond border of the muscularis propria
T4: tumor directly invades other organs or structures (T4a) tumor perforates visceral peritoneum (T4b)
Regional lymph nodes
Nx: regional lymph nodes cannot be assessed
N0: no metastasis to regional lymph nodes
N1: metastasis present in 1-3 lymph nodes
N2: metastasis present in 4 or more lymph nodes
Metastasis in non-regional lymph nodes is considered as pM1
Distant metastasis
Mx: presence of distant metastasis cannot be assessed
M0: no distant metastasis
M1: distant metastasis

RECOMMENDATIONS

47. Pathology report should include macroscopic and microscopic assessment, staging for penetration depth (T), lymph node status (N≥12 nodes), resection margins (distal, proximal, and mesocolic) status and grading (low/high grade) (SOR A) (ROVC: 99%)
48. Surgical margin status, using the R classification, should be reported (LOE II, SOR A) (ROVC: 99%)
49. Perforation at the tumor site is considered as T4a, and is of bad prognostic value (LOE III, SOR A) (ROVC: 97%)
50. In the histology report, extramural venous, tumor budding, lymphatic and perineural invasion should be recorded, as they are features of prognostic significance. At least 5 blocks of tumor should be received for confirmation of the presence or absence of extramural venous invasion (LOE III, SOR A) (ROVC: 100%)
51. Intratumoral lymphocytic infiltration is associated with MSI and is considered an independent favorable prognostic factor and should be reported. (LOE III, SOR B) (ROVC: 97%)
52. The total number and the number of involved regional lymph nodes should be reported (LOE III, SOR A) (ROVC: 100%)
53. Total number of resected lymph nodes in stage II disease, and ratio of involved over total number of involved lymph nodes as well as absolute number of negative lymph nodes in stage III disease may be related to survival (LOE III, SOR B) (ROVC: 99%)
54. Assessment of sentinel lymph node in colon cancer is associated with low sensitivity LOE III, SOR A) (ROVC: 99%)

in early adenocarcinomas developed in adenomatous polyps. Histopathology report must include: histological grade, distance of tumor from the resection margin, vascular or lymphatic invasion and depth of invasion into submucosa. According to Kikucki levels, the invasion of submucosa is graded in three levels: sm1 (superficial part of submucosa), sm2 (middle part), and sm3 (deep part). Adenocarcinoma spreading to within 1mm or less of the surgical or endoscopic resection, presence of lymphatic or vascular invasion and high-grade differentiation, as well as mid and deep third invasion of the submucosa are findings suggesting an increased risk for presence of lymph node metastasis [92,93,97].

Follow up

Background

Patient follow up depends on stage of the disease, quality of surgery, and amenability for intervention with either resection of recurrent disease or consideration of further systemic therapy. Four recent meta-analyses have shown that intensive follow up improves overall survival by 7-13% and is now considered as standard. Generally, valid assessments are 3-monthly clinical visits for the first three years, followed by 6-monthly visits for further two years with clinical examination, evaluation of long-term toxicities (polyneuropathy after oxaliplatin), and CEA testing [4,98-100].

Complete colonoscopy must be performed at initial diagnosis, after three and afterwards every five years. If the diagnostic colonoscopy was incomplete, this should be repeated at 6 months after surgery [4,99,100]. If follow-up colonoscopy shows advanced adenoma it should be repeated in one year.

In patients with high-risk disease, CT scan of the chest and abdomen every 6-12 months could be considered, although such close follow up should be confined to patients possibly amenable to resection of hepatic or pulmonary recurrence. Follow-up CT scans should be performed with the same imaging protocols and contrast phases of enhancement [4,99]. If MRI was used for the initial staging, MRI should also be used for the follow up, because CT images cannot be compared to

MRI images due to different sensitivity/specificity [4]. Liver contrast-enhanced US could substitute for abdominal CT scan regarding follow up of liver metastases, particularly in young patients with no evidence of extrahepatic disease [4,101]. Finally, routine PET-CT scanning is not recommended for surveillance [4,99].

RECOMMENDATIONS

55. Follow-up aims at detection of local and distant recurrence, metachronous colonic lesions and assessment of late post-treatment morbidity, and improves overall survival (LOE I, SOR A) (ROVC: 98%)
56. Clinical examination, long-term toxicities and serum CEA determinations are recommended to take place every 3 months for the first three years and then every 6 months for further two years (LOE II, SOR A) (ROVC: 83%)
57. Complete colonoscopy should be performed one year postoperatively and thereafter, depending on the findings, according to the guidelines for general population's surveillance (LOE II, SOR A) (ROVC: 92%)
58. If diagnostic colonoscopy is incomplete, it should be repeated at 6 months after surgery (ROVC: 91%)
59. Follow up CT scans, with the same protocol as the initial ones, should be performed in patients at high risk to develop metastatic disease every 6-12 months (ROVC: 90%)
60. MRI is used in case CT-scan is inconclusive or contra-indicated due to toxicity of the intravenous contrast agent (SOR A) (ROVC: 86%)
61. Routine PET-CT scanning is not recommended as a follow-up modality (LOE III, SOR A) (ROVC: 98%)

Concluding remarks

A MDT from members of the HeSMO developed guidelines on colon cancer management. Statements deriving from the document including background knowledge and current evidence were subjected to Delphi methodology. The guidelines strongly recommend the implementation of standardized surgery along the embryological planes to the root of the supplying vessels (CME+CVL) and pathology for the treatment of colon cancer.

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